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(54) Title: **INTERFERON-ALPHA INDUCED GENES**

(57) Abstract: The present disclosure relates to identification of genes upregulated by interferon- α administration, in particular the human genes corresponding to the cDNA sequences in GenBank designated g4586459, g2342476, g3327161 and g4529886. Determination of expression products of these genes is proposed as having utility in predicting responsiveness to treatment with interferon- α and other interferons which act at the Type 1 interferon receptor. Therapeutic use of the proteins encoded by the same genes is also envisaged.

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INTERFERON-ALPHA INDUCED GENES

Field of the Invention

5 The present invention relates to identification of genes upregulated by interferon- α (IFN- α) administration. Detection of expression products of these genes may thus find use in predicting responsiveness to IFN- α and other interferons which act at the Type 1 interferon receptor. Therapeutic use of the proteins encoded by the same genes is also envisaged.

Background of the Invention

10 IFN- α is widely used for the treatment of a number of disorders. Disorders which may be treated using IFN- α include neoplastic diseases such as leukemia, lymphomas, and solid tumours, AIDS-related Kaposi's sarcoma and viral infections such as chronic hepatitis. IFN- α has also been proposed for administration via the oromucosal route for the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic and viral disease. In particular, IFN- α has been proposed, for example, for the treatment of multiple sclerosis, leprosy, tuberculosis, 15 encephalitis, malaria, cervical cancer, genital herpes, hepatitis B and C, HIV, HPV and HSV-1 and 2. It has also been suggested for the treatment of arthritis, lupus and diabetes. Neoplastic diseases such as multiple myeloma, hairy cell leukemia, chronic myelogenous leukemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, 20 carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma and brain tumours are also suggested as being treatable by administration of IFN-via the oromucosal route, i.e. the oral route or the nasal route.

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IFN- α is a member of the Type 1 interferon family, which exert their characteristic biological activities through interaction with the Type 1 interferon receptor. Other Type 1 interferons include IFN- β , IFN- ω and IFN- τ .

5 Unfortunately, not all potential patients for treatment with a Type 1 interferon such as interferon- α , particularly, for example, patients suffering from chronic viral hepatitis, neoplastic disease and relapsing remitting multiple sclerosis, respond favourably to Type 1 interferon therapy and only a fraction of those who do respond exhibit long-term benefit. The inability of the physician to confidently predict the
10 therapeutic outcome of Type 1 interferon treatment raises serious concerns as to the cost-benefit ratio of such treatment, not only in terms of wastage of an expensive biopharmaceutical and lost time in therapy, but also in terms of the serious side effects to which the patient is exposed. Furthermore, abnormal production of IFN- α has been shown to be associated with a number of autoimmune diseases. For these
15 reasons, there is much interest in identifying Type 1 interferon responsive genes since Type 1 interferons exert their therapeutic action by modulating the expression of a number of genes. Indeed, it is the specific pattern of gene expression induced by Type 1 interferon treatment that determines whether a patient will respond favourably or not to the treatment.

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Summary of the Invention

It has now been found that the human genes corresponding to the cDNA sequences in GenBank assigned accession nos. g4586459, g2342476, g3327161 and
25 g4529886, correspond to a mouse gene upregulated by administration of IFN- α by an oromucosal route or intravenously. These human genes are thus now also designated an IFN- α upregulated gene.

The proteins corresponding to GenBank cDNAs g4586459, g2342476,
30 g3327161 and g4529886 have previously had no assigned function. These proteins (referred to below as HuIFRG-1, HuIFRG-2, HuIFRG-3 and HuIFRG-4 proteins respectively), and functional variants thereof, are now envisaged as therapeutic

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agents, in particular for use as an anti-viral, anti-tumour or immunomodulatory agent. For example, they may be used in the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic or viral disease, arthritis, diabetes, lupus, multiple sclerosis, leprosy, tuberculosis, encephalitis, malaria, cervical cancer, genital herpes, hepatitis B or C, HIV, HPV, HSV-1 or 2, or neoplastic disease such as multiple myeloma, hairy cell leukemia, chronic myelogenous leukemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma or brain tumours. In other words, such proteins may find use in treating any Type 1 interferon treatable disease.

Determination of the level of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 proteins or a naturally-occurring variant thereof, or the corresponding mRNA, in cell samples of Type 1 interferon-treated patients, e.g. patients treated with IFN- α , e.g. such as by the oromucosal route or intravenously, may also be used to predict responsiveness to such treatment. It has additionally been found that alternatively and more preferably, such responsiveness may be judged, for example, by treating a sample of human peripheral blood mononuclear cells *in vitro* with a Type 1 interferon and looking for upregulation or downregulation of an expression product, preferably mRNA, corresponding to the same gene.

According to a first aspect of the invention, there is thus provided an isolated polypeptide comprising;

- (i) the amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8;
- (ii) a variant thereof having substantially similar function, e.g. an immunomodulatory activity and/or an anti-viral activity and/or an anti-tumour activity; or

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- (iii) a fragment of (i) or (ii) which retains substantially similar function, e.g. an immunomodulatory activity and/or an anti-viral activity and/or an anti-tumour activity

for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent. As indicated above, such use may extend to any Type 1 interferon treatable disease.

According to another aspect of the invention, there is provided an isolated polynucleotide, e.g. in the form of an expression vector, which directs expression *in vivo* of a polypeptide as defined above for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent. Such a polynucleotide will typically include a sequence comprising:

- (a) the nucleic acid of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 or the coding sequence thereof;
- (b) a sequence which hybridises, e.g. under stringent conditions, to a sequence complementary to a sequence as defined in (a);
- (c) a sequence that is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or
- (d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c);

such that the polypeptide encoded by said sequence is capable of expression *in vivo*.

In a further aspect, the invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN- α treatment (such as IFN- α treatment by the oromucosal route or a parenteral route, for example, intravenously, subcutaneously or intramuscularly), which comprises determining the level of one or more proteins selected from the proteins defined by the sequences set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8, and naturally-occurring variants thereof, e.g. allelic variants, or one or more of the corresponding mRNAs, in a cell sample from said patient, e.g. a blood sample,

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wherein said sample is obtained from said patient following administration of a Type 1 interferon, e.g. IFN- α by an oromucosal route or intravenously, or is treated prior to said determining with a Type 1 interferon such as IFN- α *in vitro*. Such determining may be combined with determination of any other protein or mRNA whose expression is known to be affected in human cells by Type 1 interferon administration e.g. IFN- α administration.

The invention also provides:

- 10 - a pharmaceutical composition comprising the protein defined by the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8, or a functional variant thereof as defined above, and a pharmaceutically acceptable carrier or diluent;
- 15 - a method of treating a subject having a Type 1 interferon treatable disease, which method comprises administering to the said patient an effective amount of such a protein;
- 20 - use of such a protein in the manufacture of a medicament for use in therapy as an anti-viral or anti-tumour or immunomodulatory agent, more particularly for use in treatment of a Type 1 interferon treatable disease;
- 25 - a pharmaceutical composition comprising a polynucleotide as defined above and a pharmaceutically acceptable carrier or diluent;
- 30 - a method of treating a subject having a Type 1 interferon treatable disease, which method comprises administering to said patient an effective amount of such a polynucleotide;
- use of such a polynucleotide in the manufacture of a medicament, e.g. a vector preparation, for use in therapy as an anti-viral, anti-tumour or immunomodulatory agent, more particularly for use in treating a Type 1 interferon treatable disease;
- a polynucleotide capable of expressing *in vivo* an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8, or a naturally-occurring variant of said coding sequence, for use in therapeutic

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treatment of a human or non-human animal and pharmaceutical compositions comprising such a polynucleotide in combination with a pharmaceutically acceptable carrier or diluent;
an antibody to the protein defined by the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6 or SEQ ID NO: 8 for use in therapeutic treatment of a human or animal body and corresponding pharmaceutical compositions.

Brief description of the Sequences

SEQ. ID. No.1 is the amino acid sequence of human protein HuIFRG-1 and its encoding cDNA.

SEQ. ID. No.2 is the amino acid sequence alone of HuIFRG-1 protein.

SEQ. ID. No.3 is the amino acid sequence of human protein HuIFRG-2 and its encoding cDNA.

SEQ. ID. No.4 is the amino acid sequence alone of HuIFRG-2 protein.

SEQ. ID. No.5 is the amino acid sequence of human protein HuIFRG-3 and its encoding cDNA.

SEQ. ID. No.6 is the amino acid sequence alone of HuIFRG-3 protein.

SEQ. ID. No.7 is the amino acid sequence of human protein HuIFRG-4 and its encoding cDNA.

SEQ. ID. No.8 is the amino acid sequence alone of HuIFRG-4 protein.

Detailed Description of the Invention

As indicated above, human proteins HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 and functional variants thereof are now envisaged as therapeutically useful agents, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent.

A variant of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein for this purpose may be a naturally-occurring variant, either an allelic variant or a species

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variant, which has substantially the same functional activity as HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein and is also upregulated in response to administration of IFN- α , e.g. oromucosal or intravenous administration of IFN- α . Alternatively, a variant of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein for therapeutic use may comprise a sequence which varies from SEQ. ID. No. 2 but which is a non-natural mutant.

The term "functional variant" refers to a polypeptide which has the same essential character or basic function of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein. The essential character of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein may be deemed to be as an immunomodulatory polypeptide. A functional variant polypeptide may show additionally or alternatively anti-viral activity and/or anti-tumour activity.

Desired anti-viral activity may, for example, be tested for as follows. A sequence encoding a variant to be tested is cloned into a retroviral vector such as a retroviral vector derived from the Moloney murine leukemia virus (MoMuLV) containing the viral packaging signal ψ , and a drug-resistance marker. A pantropic packaging cell line containing the viral *gag*, and *pol*, genes is then co-transfected with the recombinant retroviral vector and a plasmid, pVSV-G, containing the vesicular stomatitis virus envelope glycoprotein in order to produce high-titre infectious replication-incompetent virus (Burns *et al.*, Proc. Natl. Acad. Sci. USA 84, 5232-5236). The infectious recombinant virus is then used to transfect interferon sensitive fibroblasts or lymphoblastoid cells and cell lines that stably express the variant protein are then selected and tested for resistance to virus infection in a standard interferon bio-assay (Tovey *et al.*, Nature, 271, 622-625, 1978). Growth inhibition using a standard proliferation assay (Mosmann, T., J. Immunol. Methods, 65, 55-63, 1983) and expression of MHC class I and class II antigens using standard techniques may also be determined.

A desired functional variant of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein may consist essentially of the sequence of SEQ ID NO: 2, SEQ

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ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8. A functional variant of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 may be a polypeptide which has a least 60% to 70% identity, preferably at least 80% or at least 90% and particularly preferably at least 95%, at least 97% or at least 99% identity with the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 over a region of at least 20, preferably at least 30, for instance at least 100 contiguous amino acids or over the full length of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8. Methods of measuring protein identity are well known in the art.

Amino acid substitutions may be made, for example from 1, 2 or 3 to 10, 20 or 30 substitutions. Conservative substitutions may be made, for example according to the following Table. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other.

ALIPHATIC	Non-polar	G A P
		I L V
	Polar-uncharged	C S T M
		N Q
	Polar-charged	D E
		K R
AROMATIC		H F W Y

Variant polypeptide sequences for therapeutic use in accordance with the invention may be shorter polypeptide sequences, for example, a peptide of at least 20 amino acids or up to 50, 60, 70, 80, 100, 150 or 200 amino acids in length is

considered to fall within the scope of the invention provided it retains appropriate biological activity of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein. In particular, but not exclusively, this aspect of the invention encompasses the situation when the variant is a fragment of a complete naturally-occurring protein sequence.

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Variant polypeptides for therapeutic use in accordance with the invention may be chemically modified, e.g. post-translationally modified. For example, they may be glycosylated and/or comprise modified amino acid residues. They may also be modified by the addition of a sequence either at the N-terminus and/or C-terminus. Polypeptides for therapeutic use in accordance with the invention may be made synthetically or by recombinant means. Such polypeptides may be modified to include non-naturally occurring amino acids, e.g. D amino acids. Variant polypeptides for use in accordance with the invention may have modifications to increase stability *in vitro* and/or *in vivo*. When the polypeptides are produced by synthetic means, such modifications may be introduced during production. The polypeptides may also be modified following either synthetic or recombinant production.

A number of side chain modifications are known in the protein modification art and may be present in variants for therapeutic use according to the invention. Such modifications include, for example, modifications of amino acids by reductive alkylation by reaction with an aldehyde followed by reduction with NaBH_4 , amidination with methylacetimidate or acylation with acetic anhydride.

Polypeptides for use in accordance with the invention will be in substantially isolated form. It will be understood that the polypeptides may be mixed with carriers or diluents which will not interfere with the intended purpose of the polypeptide and still be regarded as substantially isolated.

30 Polynucleotide therapy

As an alternative to administration of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein, or a functional variant thereof as described above, an isolated polynucleotide may be administered, e.g. in the form of an expression vector such as a viral vector, which directs expression of the desired polypeptide *in vivo*. Hence, as indicated above, in a further embodiment the invention provides an isolated polynucleotide, which directs expression *in vivo* of a polypeptide as defined above, which polynucleotide includes a sequence comprising:

- (a) the nucleic acid of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 or the coding sequence thereof;
- 10 (b) a sequence which hybridises, e.g. under stringent conditions, to a sequence complementary to a sequence as defined in (a);
- (c) a sequence that is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or
- (e) a sequence having at least 60% identity to a sequence as defined in
15 (a), (b) or (c)

for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent.

Preferably, such a polynucleotide will be a DNA. The coding sequence for HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein or a variant thereof may be provided by a cDNA sequence or a genomic DNA sequence. Polynucleotides comprising an appropriate coding sequence can be isolated from human cells or synthesised according to methods well known in the art, as described by way of example in Sambrook *et al.* (1989) Molecular Cloning: A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory Press.

Polynucleotides for use in accordance with the invention may include within them synthetic or modified nucleotides. A number of different types of modification to polynucleotides are known in the art. These include methylphosphonate and phosphothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. Such modifications may be incorporated to enhance the *in vivo* activity or life span of the polynucleotide as a therapeutic agent.

Typically, a polynucleotide for use in accordance with the invention will include a sequence of nucleotides, which may preferably be a contiguous sequence of nucleotides, which is capable of hybridising under selective conditions to the complement of the coding sequence of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7. Such hybridisation will occur at a level significantly above background. Background hybridisation may occur, for example, because of other cDNAs present in a cDNA library. The signal level generated by the interaction between a desired coding sequence and the complement of the coding sequence of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 will typically be at least 10 fold, preferably at least 100 fold, as intense as interactions between other polynucleotides and the target sequence. The intensity of interaction may be measured, for example, by radiolabelling the nucleic acid selected for probing, e.g. with ^{32}P . Selective hybridisation may typically be achieved using conditions of low stringency (0.3M sodium chloride and 0.03M sodium citrate at about 40°C), medium stringency (for example, 0.3M sodium chloride and 0.03M sodium citrate at about 50°C) or high stringency (for example, 0.03M sodium chloride and 0.003M sodium citrate at about 60°C).

The coding sequence of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 may be modified for incorporation into a polynucleotide as defined above by nucleotide substitutions, for example from 1, 2 or 3 to 10, 25, 50 or 100 substitutions. Degenerate substitutions may, for example, be made and/or substitutions may be made which would result in a conservative amino acid substitution when the modified sequence is translated, for example as shown in the table above. The coding sequence of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 may alternatively or additionally be modified by one or more insertions and/or deletions and/or by an extension at either or both ends provided it encodes a polypeptide with the appropriate functional activity compared to HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein.

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A nucleotide sequence capable of selectively hybridising to the complement of SEQ. ID. NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7, or at least the coding sequence thereof, will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% or 97%, homologous to such a DNA sequence.

5 This homology may typically be over a region of at least 20, preferably at least 30, for instance at least 40, 60 or 100 or more contiguous nucleotides of the said DNA sequence.

Any combination of the above mentioned degrees of homology and minimum
10 size may be used to define nucleic acids comprising desired coding sequences, with the more stringent combinations (i.e. higher homology over longer lengths) being preferred. Thus for example a polynucleotide which is at least 80% homologous over 25, preferably over 30 nucleotides may be found suitable, as may be a polynucleotide which is at least 90% homologous over 40 nucleotides.

15 Homologues of polynucleotide or protein sequences as referred to herein may be determined in accordance with well-known means of homology calculation, e.g. protein homology may be calculated on the basis of amino acid identity (sometimes referred to as "hard homology"). For example the UWGCG Package provides the
20 BESTFIT program which can be used to calculate homology, for example used on its default settings, (Devereux *et al.* (1984) *Nucleic Acids Research* 12, p387-395). The PILEUP and BLAST algorithms can be used to calculate homology or line up sequences or to identify equivalent or corresponding sequences, typically used on their default settings, for example as described in Altschul S. F. (1993) *J Mol Evol*
25 36:290-300; Altschul, S, F *et al.* (1990) *J Mol Biol* 215:403-10.

Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pair (HSPs) by
30 identifying short words of length W in the query sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighbourhood word score threshold

(Altschul *et al*, supra). These initial neighbourhood word hits act as seeds for initiating searches to find HSP=s containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extensions for the word hits in each direction are halted when: the
5 cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a word length (W) of 11, the
10 BLOSUM62 scoring matrix (see Henikoff and Henikoff (1992) *Proc. Natl. Acad. Sci. USA* 89: 10915-10919) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

The BLAST algorithm performs a statistical analysis of the similarity
15 between two sequences; see e.g., Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90: 5873-5787. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a sequence is considered similar to another
20 sequence if the smallest sum probability in comparison of the first sequence to the second sequence is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

As indicated above, a polynucleotide for use in accordance with the
25 invention in substitution for direct administration of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein or a functional variant thereof may preferably be in the form of an expression vector. Expression vectors are routinely constructed in the art of molecular biology and may, for example, involve the use of plasmid DNA and appropriate initiators, promoters, enhancers and other elements, such as for example
30 polyadenylation signals which may be necessary, and which are positioned in the correct orientation, in order to allow for protein expression. Such vectors may be viral vectors. Examples of suitable viral vectors include herpes simplex viral vectors.

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replication-defective retroviruses, including lentiviruses, adenoviruses, adeno-associated virus, HPV viruses (such as HPV-16 and HPV-18) and attenuated influenza virus vectors. Other suitable vectors would be apparent to persons skilled in the art. By way of further example in this regard reference is made again to
5 Sambrook *et al.*, 1989 (*supra*).

A polynucleotide capable of expressing *in vivo* an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ. ID. No. 2, or a naturally-occurring variant thereof, for use in therapeutic treatment of a human or
10 non-human animal is also envisaged as constituting an additional aspect of the invention. Again, such a polynucleotide may preferably be in the form of an expression vector. Such a polynucleotide will find use in treatment of diseases associated with upregulation of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein.

15 It will be appreciated that antibodies to HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein and antigen-binding fragments thereof may find similar use.

Pharmaceutical compositions

20 A polypeptide for use in accordance with the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. The pharmaceutical carrier or diluent may be, for example, an isotonic solution. For example, solid oral forms may contain, together with the active compound, diluents,
25 e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate and or polyethelene glycols; binding agents, e.g. starches, arabic gums, gelatin, methyl cellulose, carboxymethylcellulose or polyvinyl pyrrolidone; desegregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs;
30 sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known

manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or
5 saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methyl cellulose, carboxymethylcellulose, or
10 polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

15 Solutions for intravenous injection or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The dose of polypeptide for use in accordance with the invention may be
20 determined according to various parameters, especially according to the substance used: the age, weight and condition of the patient to be treated; the route of administration; and the required regimen. A physician will be able to determine the required route of administration and dosage for any particular patient. A typical daily dose is from about 0.1 to 50 mg per kg, preferably from about 0.1mg/kg to
25 10mg/kg of body weight, according to the activity of the specific active compound, the age, weight and condition of the subject to be treated, and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

A polynucleotide for use in accordance with the invention will also typically
30 be formulated for administration with a pharmaceutically acceptable carrier or diluent. Such a polynucleotide may be administered by any known technique whereby expression of the desired polypeptide can be attained *in vivo*. For example,

the polynucleotide may be delivered intradermally, subcutaneously, or intramuscularly. Alternatively, the polynucleotide may be delivered across the skin using a particle-mediated delivery device. A polynucleotide for use in accordance with the invention may be administered by intranasal or oral administration.

5

A non-viral vector for use in accordance with the invention may be packaged into liposomes or into surfactant. Uptake of nucleic acid constructs for use in accordance with the invention may be enhanced by several known transfection techniques, for example those including the use of transfection agents. Examples of these agents include cationic agents, for example calcium phosphate and DEAE dextran and lipofectants, for example lipopfectam and transfectam. The dosage of the nucleic acid to be administered can be varied. Typically, the nucleic acid is administered in the range of from 1pg to 1mg, preferably from 1pg to 10 μ g nucleic acid for particle-mediated gene delivery and from 10 μ g to 1 mg for other routes.

15

Prediction of Type 1 interferon responsiveness

As also indicated above, in a still further aspect the present invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN- α treatment such as IFN- α treatment by an oromucosal route or intravenously, which comprises determining the level of one or more of HuIFRG-1, HuIFRG-2, HuIFRG-3, HuIFRG-4 protein and naturally-occurring variants thereof, or one or more corresponding mRNAs, in a cell sample from said patient, wherein said sample is taken from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon *in vitro*.

25

Preferably, the Type 1 interferon for testing responsiveness will be the Type 1 interferon selected for treatment. It may be administered by the proposed treatment route and at the proposed treatment dose. Preferably, the subsequent sample analysed may be, for example, a blood sample or a sample of peripheral blood mononuclear cells (PBMCs) isolated from a blood sample.

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More conveniently and preferably, a sample obtained from the patient comprising PBMCs isolated from blood may be treated *in vitro* with a Type 1 interferon, e.g. at a dosage range of about 1 to 10,000 IU/ml. Such treatment may be for a period of hours, e.g. about 7 to 8 hours. Preferred treatment conditions for such *in vitro* testing may be determined by testing PBMCs taken from normal donors with the same interferon and looking for upregulation of an appropriate expression product. Again, the Type 1 interferon employed will preferably be the Type 1 interferon proposed for treatment of the patient, e.g. recombinant IFN- α . PBMCs for such testing may be isolated in conventional manner from a blood sample using Ficoll-Hypaque density gradients. An example of a suitable protocol for such *in vitro* testing of Type 1 interferon responsiveness is provided in Example 6 below.

The sample, if appropriate after *in vitro* treatment with a Type 1 interferon, may be analysed for the level of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein or a naturally-occurring variant thereof. This may be done using an antibody or antibodies capable of specifically binding one or more of HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein and naturally-occurring variants thereof, eg. allelic variants thereof. Preferably, however, the sample will be analysed for mRNA encoding HuIFRG-1, HuIFRG-2, HuIFRG-3 or HuIFRG-4 protein or a naturally-occurring variant thereof. Such mRNA analysis may employ any of the techniques known for detection of mRNAs, e.g. Northern blot detection or mRNA differential display. A variety of known nucleic acid amplification protocols may be employed to amplify any mRNA of interest present in the sample, or a portion thereof, prior to detection. The mRNA of interest, or a corresponding amplified nucleic acid, may be probed for using a nucleic acid probe attached to a solid support. Such a solid support may be a micro-array carrying probes to determine the level of further mRNAs or amplification products thereof corresponding to Type 1 interferon upregulated genes, e.g. such genes identified as upregulated in response to oromucosal or intravenous administration of IFN- α . Methods for constructing such micro-arrays (also referred to commonly as nucleic acid, probe or DNA chips) are well-known (see, for example, EP-B 0476014 and 0619321 of Affymax

Technologies N.V. and Nature Genetics Supplement January 1999 entitled "The Chipping Forecast").

The following examples illustrate the invention:

Examples

Example 1

Previous experiments had shown that the application of 5 μ l of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using 125 I-labelled recombinant human IFN- γ 1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10 μ g of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μ g/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) 162, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, 257, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and

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"RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse-transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α -³³P dATP (3,000 Ci/mmol). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to autoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfi* I site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used

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to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4586459. The corresponding polypeptide sequence is GenBank sequence
5 g4586460, not assigned in GenBank any function.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN- α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN- α . A similar
10 result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accession no. g4586459 when intravenous administration of IFN- α is carried out as described in Example 5 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse
15 genes found to be upregulated in response to oromucosal and intravenous administration of IFN- α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN- α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ ID NO: 1 when human peripheral blood mononuclear cells are treated with IFN- α as described
20 in Example 6 below.

Example 2

Previous experiments had shown that the application of 5 μ l of crystal violet
25 to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ¹²⁵I-labelled recombinant human IFN- α 1-8 applied in the same manner. The same
30 method of administration was employed to effect oromucosal administration in the studies which are described below.

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Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10 μ g of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μ g/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) 162, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, 257, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μ g was reverse-transcribed in 100 μ l of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μ l of the reverse transcription sample in 10 μ l of amplification mixture containing *Taq* DNA polymerase and α -³³P dATP (3,000 Ci/mmol). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to autoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfi* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g2342476. The corresponding polypeptide sequence is GenBank sequence g2342477, not assigned in GenBank any function.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN- α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN- α . A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g2342476 when intravenous administration of IFN- α is carried out as described in Example 5 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN- α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN- α *in vitro*. The same result is

anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 3 when human peripheral blood mononuclear cells are treated with IFN- α as described in Example 6 below.

5 Example 3

Previous experiments had shown that the application of 5 μ l of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the
10 oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using 125 I-labelled recombinant human IFN- γ 1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

15 Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10 μ g of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μ g/ml of bovine serum
20 albumin (BSA); or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display
25 Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and
30 "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μ g was reverse-transcribed in 100 μ l of reaction buffer using either one or the other of the

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three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The
5 amplification was performed with only 1 μ l of the reverse transcription sample in 10 μ l of amplification mixture containing *Taq* DNA polymerase and α -³³P dATP (3,000 Ci/mmol). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and
10 exposed to autoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

15 Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3
20 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

25 Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used
30 to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence

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g3327161. The corresponding polypeptide sequence is GenBank sequence g3327162, not assigned in GenBank any function.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN- α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN- α . A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g3327161 when intravenous administration of IFN- α is carried out as described in Example 5 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN- α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN- α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 5 when human peripheral blood mononuclear cells are treated with IFN- α as described in Example 6 below.

Example 4

Previous experiments had shown that the application of 5 μ l of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using 125 I-labelled recombinant human IFN- α 1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10 μ g of recombinant human interleukin 15 (IL-15)

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purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) 162, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, 257, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α -³³P dATP (3,000 Ci/mmol). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to autoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the

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Sfr 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

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Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

15 One such cDNA was found to correspond to GenBank cDNA sequence g4529886. The corresponding polypeptide sequence is GenBank sequence g4529888, not assigned in GenBank any function.

20 Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN- α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN- α . A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accession no. g4529886 when intravenous administration of IFN- α is carried out as described in Example 5 below.

25

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN- α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN- α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 7 when human peripheral blood mononuclear cells are treated with IFN- α as described in Example 6 below.

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Example 5

Intravenous administration of IFN- α

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Male DBA/2 mice are injected intravenously with 100,000 IU of recombinant murine IFN- α purchased from Life Technologies Inc. in 200 μ l of PBS or treated with an equal volume of PBS alone. Eight hours later the animals are sacrificed by cervical dislocation and the spleen was removed using conventional procedures.

10

Total RNA was extracted by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) 162, 156-159) and 10.0 μ g of total RNA per sample is subjected to Northern blotting in the presence of glyoxal and hybridised with a cDNA probe for the mRNA of interest as described by Dandoy-Dron et al. (J. Biol. Chem. (1998) 273, 7691-7697). The blots are first exposed to autoradiography and then quantified

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using a PhosphorImager according to the manufacturer's instructions.

Example 6

Testing Type 1 interferon responsiveness *in vitro*

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Human peripheral blood mononuclear cells (PBMC) from normal donors are isolated on Ficoll-Hypaque density gradients and treated *in vitro* with 10,000 IU of recombinant human IFN- α 2 (intron A from Schering-Plough) in PBS or with an equal volume of PBS alone. Eight hours later the cells are centrifuged (800 x g for 10

25

minutes) and the cell pellet recovered. Total RNA is extracted from the cell pellet by the method of Chomczynski and Sacchi and 10.0 μ g of total RNA per sample is subjected to Northern blotting as described in Example 5 above.

The same procedure can be used to predict Type 1 interferon responsiveness

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using PBMC taken from a patient proposed to be treated with a Type 1 interferon.

CLAIMS:

1. An isolated polypeptide comprising
 - (i) the amino acid sequence of any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8;
 - (ii) a variant thereof having substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity; or
 - (iii) a fragment of a sequence as defined in (i) or (ii) which retains substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activityfor use in therapeutic treatment of a human or non-human animal.
2. An isolated polynucleotide which directs expression *in vivo* of a polypeptide as defined in claim 1 for use in therapeutic treatment of a human or non-human animal.
3. An isolated polynucleotide as claimed in claim 2 which includes a sequence comprising:
 - (a) the nucleic acid of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 or the coding sequence thereof;
 - (b) a sequence which hybridises to a sequence complementary to a sequence as defined in (a);
 - (c) a sequence which is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or
 - (d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c);such that the polypeptide encoded by said sequence is capable of expression *in vivo*.

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4. A polypeptide or polynucleotide as claimed in any one of claims 1 to 3 for use as an anti-viral, anti-tumour or immunomodulatory agent.
5. A polypeptide or polynucleotide as claimed in claim 4 for use in treating a Type 1 interferon treatable disease.
6. A pharmaceutical composition comprising a polypeptide or polynucleotide as claimed in any one of claims 1 to 5 and a pharmaceutically acceptable carrier or diluent.
7. Use of a polypeptide or polynucleotide as defined in any one of claims 1 to 5 in the preparation of a medicament for use in therapy as an anti-viral, anti-tumour or immunomodulatory agent.
8. A method of treating a patient having a Type 1 interferon treatable disease, which comprises administering to said patient an effective amount of a polypeptide or polynucleotide as defined in any one of claims 1 to 5.
9. A method of predicting responsiveness of a patient to treatment with a Type 1 interferon, which comprises determining the level of one or more proteins selected from the proteins defined by the sequences set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 and naturally-occurring variants thereof, or one or more of the corresponding mRNAs, in a cell sample from said patient, wherein said sample is obtained from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon *in vitro*.
10. A method as claimed in claim 9 wherein the interferon administered prior to obtaining said sample or used to treat said sample *in vitro* is the interferon proposed for treatment.

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11. A method as claimed in claim 9 or 10 wherein a sample comprising peripheral blood mononuclear cells isolated from a blood sample of the patient is treated with a Type 1 interferon *in vitro*.
12. A method as claimed in any one of claims 9 to 11 wherein said determining comprises determining the level of mRNA encoding the protein defined by the sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 or a naturally-occurring variant of said protein.
13. A polynucleotide capable of expressing *in vivo* an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 or a naturally-occurring variant of said coding sequence for use in therapeutic treatment of a human or non-human animal.
14. An antibody to the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8 for use in therapeutic treatment of a human or animal body.

caa gaa atg att gca ata cca cct cag gcc att aag tgc tgt tta gca 432
 Gln Glu Met Ile Ala Ile Pro Pro Gln Ala Ile Lys Cys Cys Leu Ala
 130 135 140

gat ctt cca caa tct att ggc atg tgg aca cca gat gca gtg ctg tgg 480
 Asp Leu Pro Gln Ser Ile Gly Met Trp Thr Pro Asp Ala Val Leu Trp
 145 150 155 160

tta aga gat tct gtt ttg aat tgc tcg gac tgt agc att aag gtt aca 528
 Leu Arg Asp Ser Val Leu Asn Cys Ser Asp Cys Ser Ile Lys Val Thr
 165 170 175

aaa gtg gat gaa acc aga ggg atc gca cat gtt tat tta ttt acc cct 576
 Lys Val Asp Glu Thr Arg Gly Ile Ala His Val Tyr Leu Phe Thr Pro
 180 185 190

aag aac ttc cct gac cct cat cgc agt att aat cgc cag att aca aat 624
 Lys Asn Phe Pro Asp Pro His Arg Ser Ile Asn Arg Gln Ile Thr Asn
 195 200 205

gca gac ttg tgg aag cat cag aag gat gtg ttt ttg agt gcc ata tcc 672
 Ala Asp Leu Trp Lys His Gln Lys Asp Val Phe Leu Ser Ala Ile Ser
 210 215 220

agt gga gct gac tct ccc aac agc aaa aat ggc aac atg ccc atg tcg 720
 Ser Gly Ala Asp Ser Pro Asn Ser Lys Asn Gly Asn Met Pro Met Ser
 225 230 235 240

ggc aac act gga gag aat ttc aga aag aac ctc aca gat gtc atc aaa 768
 Gly Asn Thr Gly Glu Asn Phe Arg Lys Asn Leu Thr Asp Val Ile Lys
 245 250 255

aag tcc atg gtg gac cat acg agc gct ttc tcc aca gag gaa ctg cca 816
 Lys Ser Met Val Asp His Thr Ser Ala Phe Ser Thr Glu Glu Leu Pro
 260 265 270

cct cct gtc cac tta tca aag cca ggc gaa cac atg gat gtg tat gtg 864
 Pro Pro Val His Leu Ser Lys Pro Gly Glu His Met Asp Val Tyr Val
 275 280 285

cct gtg gcc tgt cac cca ggc tac ttc gtc atc cag cct tgg cag gag 912
 Pro Val Ala Cys His Pro Gly Tyr Phe Val Ile Gln Pro Trp Gln Glu
 290 295 300

ata cat aag ttg gaa gtt ctg atg gaa gag atg att cta tat tac agc 960
 Ile His Lys Leu Glu Val Leu Met Glu Glu Met Ile Leu Tyr Tyr Ser
 305 310 315 320

gtg tct gaa gag cgc cac ata gca gtg gag aaa gac caa gtg tat gct 1008
 Val Ser Glu Glu Arg His Ile Ala Val Glu Lys Asp Gln Val Tyr Ala
 325 330 335

gca aaa gtg gaa aat aag tgg cac agg gtg ctt tta aaa gga atc ctg 1056
 Ala Lys Val Glu Asn Lys Trp His Arg Val Leu Leu Lys Gly Ile Leu
 340 345 350

-3-

acc aat gga ctg gta tct gtg tat gag ctg gat tat ggc aaa cac gaa 1104
 Thr Asn Gly Leu Val Ser Val Tyr Glu Leu Asp Tyr Gly Lys His Glu
 355 360 365

tta gtc aac ata aga aaa gta cag ccc cta gtg gac atg ttc cga aag 1152
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 370 375 380

ctg ccc ttc caa gca gtc aca gct caa ctt gca gga gtg aag tgc aac 1200
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 385 390 395 400

cag tgg tct gag gag gct tct atg gtg ttt cga aat cat gtg gag aag 1248
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 405 410 415

aaa cct ctg gtg gca ctg gtg cag aca gtc att gaa aat gct aac cct 1296
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 420 425 430

tgg gac cgg aaa gta gtg gtc tac tta gtg gac aca tgc ttg cca gac 1344
 Trp Asp Arg Lys Val Val Val Tyr Leu Val Asp Thr Ser Leu Pro Asp
 435 440 445

acc gat acc tgg att cat gat ttt atg tca gag tat ctg ata gag ctt 1392
 Thr Asp Thr Trp Ile His Asp Phe Met Ser Glu Tyr Leu Ile Glu Leu
 450 455 460

tca aaa gtt aat taa tgactgcctc tgaacacctg acaactaatt cagatttttt 1447
 Ser Lys Val Asn
 465

agcaataaca aaatgtagta ggcttaaaaa aaatcttaac tctgctacat ggctctgact 1507

gctgtggggg attgaaaaga atatgcttat gtttgatgaa agatatttaa caagtittgt 1567

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aaaaatgttt atc 1640

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Ser Asp Gly Thr Leu Tyr Cys Gln Val Pro Cys Lys Gly Leu Asn Lys
 35 40 45

-4-

Leu Ser Asp Leu Leu Arg Lys Ile Glu Asp Tyr Phe His Cys Lys His
 50 55 60

Met Thr Ser Glu Cys Phe Val Ser Leu Pro Phe Cys Gly Lys Ile Cys
 65 70 75 80

Leu Phe His Cys Lys Gly Lys Trp Leu Arg Val Glu Ile Thr Asn Val
 85 90 95

His Ser Ser Arg Ala Leu Asp Val Gln Phe Leu Asp Ser Gly Thr Val
 100 105 110

Thr Ser Val Lys Val Ser Glu Leu Arg Glu Ile Pro Pro Arg Phe Leu
 115 120 125

Gln Glu Met Ile Ala Ile Pro Pro Gln Ala Ile Lys Cys Cys Leu Ala
 130 135 140

Asp Leu Pro Gln Ser Ile Gly Met Trp Thr Pro Asp Ala Val Leu Trp
 145 150 155 160

Leu Arg Asp Ser Val Leu Asn Cys Ser Asp Cys Ser Ile Lys Val Thr
 165 170 175

Lys Val Asp Glu Thr Arg Gly Ile Ala His Val Tyr Leu Phe Thr Pro
 180 185 190

Lys Asn Phe Pro Asp Pro His Arg Ser Ile Asn Arg Gln Ile Thr Asn
 195 200 205

Ala Asp Leu Trp Lys His Gln Lys Asp Val Phe Leu Ser Ala Ile Ser
 210 215 220

Ser Gly Ala Asp Ser Pro Asn Ser Lys Asn Gly Asn Met Pro Met Ser
 225 230 235 240

Gly Asn Thr Gly Glu Asn Phe Arg Lys Asn Leu Thr Asp Val Ile Lys
 245 250 255

Lys Ser Met Val Asp His Thr Ser Ala Phe Ser Thr Glu Glu Leu Pro
 260 265 270

Pro Pro Val His Leu Ser Lys Pro Gly Glu His Met Asp Val Tyr Val
 275 280 285

Pro Val Ala Cys His Pro Gly Tyr Phe Val Ile Gln Pro Trp Gln Glu
 290 295 300

Ile His Lys Leu Glu Val Leu Met Glu Glu Met Ile Leu Tyr Tyr Ser
 305 310 315 320

Val Ser Glu Glu Arg His Ile Ala Val Glu Lys Asp Gln Val Tyr Ala
 325 330 335

Ala Lys Val Glu Asn Lys Trp His Arg Val Leu Leu Lys Gly Ile Leu
 340 345 350

-5-

Thr Asn Gly Leu Val Ser Val Tyr Glu Leu Asp Tyr Gly Lys His Glu
355 360 365

Leu Val Asn Ile Arg Lys Val Gln Pro Leu Val Asp Met Phe Arg Lys
370 375 380

Leu Pro Phe Gln Ala Val Thr Ala Gln Leu Ala Gly Val Lys Cys Asn
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Gln Trp Ser Glu Glu Ala Ser Met Val Phe Arg Asn His Val Glu Lys
405 410 415

Lys Pro Leu Val Ala Leu Val Gln Thr Val Ile Glu Asn Ala Asn Pro
420 425 430

Trp Asp Arg Lys Val Val Val Tyr Leu Val Asp Thr Ser Leu Pro Asp
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Ser Lys Val Asn
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tttggaaga atg gaa gct gat gca tct gtt gac atg ttt tcc aaa gtc ctg 171
Met Glu Ala Asp Ala Ser Val Asp Met Phe Ser Lys Val Leu
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gag cat cag ctg ctt cag act acc aaa ctg gtg gaa gaa cat ttg gat 219
Glu His Gln Leu Leu Gln Thr Thr Lys Leu Val Glu Glu His Leu Asp
15 20 25 30

tct gaa att caa aaa ctg gat cag atg gat gag gat gaa ttg gaa cgc 267
Ser Glu Ile Gln Lys Leu Asp Gln Met Asp Glu Asp Glu Leu Glu Arg
35 40 45

ctt aaa gaa aag aga ctc cag gca cta agg aaa gct caa cag cag aaa 315
Leu Lys Glu Lys Arg Leu Gln Ala Leu Arg Lys Ala Gln Gln Gln Lys
50 55 60

caa gaa tgg ctt t aaa gga cat ggg gaa tac aga gaa atc cct agt 363
 Gln Glu Trp Leu Ser Lys Gly His Gly Glu Tyr Arg Glu Ile Pro Ser
 65 70 75

gaa aga gac ttt ttt caa gaa gtc aag gag agt gaa aat gtg gtt tgc 411
 Glu Arg Asp Phe Phe Gln Glu Val Lys Glu Ser Glu Asn Val Val Cys
 80 85 90

cat ttc tac aga gac tcc aca ttc agg tgt aaa ata cta gac aga cat 459
 His Phe Tyr Arg Asp Ser Thr Phe Arg Cys Lys Ile Leu Asp Arg His
 95 100 105 110

ctg gca ata ttg tcc aag aaa cac ctc gag acc aat ttt ttg aag ctg 507
 Leu Ala Ile Leu Ser Lys Lys His Leu Thr Asn Phe Leu Lys Leu
 115 120 125

aat gtg gaa aaa gca cct ttc ctt tgt gag aga ctg cat atc aaa gtc 555
 Asn Val Glu Lys Ala Pro Phe Leu Cys Glu Arg Leu His Ile Lys Val
 130 135 140

att ccc aca cta gca ctg cta aaa gat ggg aaa aca caa gat tat gtt 603
 Ile Pro Thr Leu Ala Leu Leu Lys Asp Gly Lys Thr Gln Asp Tyr Val
 145 150 155

gtt ggg ttt act gac cta gga aat aca gat gac ttc acc aca gaa act 651
 Val Gly Phe Thr Asp Leu Gly Asn Thr Asp Asp Phe Thr Thr Glu Thr
 160 165 170

tta gaa tgg agg ctc ggt tct tct gac att ctt aat tac agt gga aat 699
 Leu Glu Trp Arg Leu Gly Ser Ser Asp Ile Leu Asn Tyr Ser Gly Asn
 175 180 185 190

tta atg gag cca cca ttt cag aac caa aag aaa ttt gga aca aac ttc 747
 Leu Met Glu Pro Pro Phe Gln Asn Gln Lys Lys Phe Gly Thr Asn Phe
 195 200 205

aca aag ctg gaa aag aaa act atg cga gga aag aaa tat gat tca gac 795
 Thr Lys Leu Glu Lys Lys Thr Met Arg Gly Lys Lys Tyr Asp Ser Asp
 210 215 220

tct gat gat gat tag agctcaataa ttctttgtaa attgtctttt tttttctgct 850
 Ser Asp Asp Asp

tcagatttaa atgtgttttt aaaattctat taatgtctat acattggtca cctaaatact 910

catattctcg agttttatac agttgtatca catcgaaaag tgtctttact gttttctgtg 970

tggccatcat gtttaagttg aggaaactca gticttaaat tatctgggaa gggctctggat 1030

tctctatttt tgagattgac tttatcacia tatgattctt acatctttat accatttaca 1090

attgtgtttt agatctacag agttagaat tcgraaacta ttccaggact aattcttaat 1150

cggcattatt tatacaagag gtcaagtaac atttactagc gcaatactgc acttgtaaatt 1210

gaattataaa cgctcttctg gaatatattt aaataaccat taaagaactg cttattcatt 1270

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ctggacactg catgtigatg ttgaatcaac tgatgccagc agaaagctat ttgatttgt 1330

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35 40 45Glu Lys Arg Leu Gln Ala Leu Arg Lys Ala Gln Gln Gln Lys Gln Glu
50 55 60Trp Leu Ser Lys Gly His Gly Glu Tyr Arg Glu Ile Pro Ser Glu Arg
65 70 75 80Asp Phe Phe Gln Glu Val Lys Glu Ser Glu Asn Val Val Cys His Phe
85 90 95Tyr Arg Asp Ser Thr Phe Arg Cys Lys Ile Leu Asp Arg His Leu Ala
100 105 110Ile Leu Ser Lys Lys His Leu Glu Thr Asn Phe Leu Lys Leu Asn Val
115 120 125Glu Lys Ala Pro Phe Leu Cys Glu Arg Leu His Ile Lys Val Ile Pro
130 135 140Thr Leu Ala Leu Leu Lys Asp Gly Lys Thr Gln Asp Tyr Val Val Gly
145 150 155 160Phe Thr Asp Leu Gly Asn Thr Asp Asp Phe Thr Thr Glu Thr Leu Glu
165 170 175Trp Arg Leu Gly Ser Ser Asp Ile Leu Asn Tyr Ser Gly Asn Leu Met
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ttc ggt gcg ggg gac gag gac gac acc gat ttc ctc tcg ccg agc ggc  96
Phe Gly Ala Gly Asp Glu Asp Asp Thr Asp Phe Leu Ser Pro Ser Gly
      20             25             30

ggg gcc aga ttg gcc tca ctt ttt gga ctg gat cag gca gct gct ggc  144
Gly Ala Arg Leu Ala Ser Leu Phe Gly Leu Asp Gln Ala Ala Ala Gly
      35             40             45

cat gga aat gaa ttt ttc cag tac aca gcc cca aaa cag cct aag aaa  192
His Gly Asn Glu Phe Phe Gln Tyr Thr Ala Pro Lys Gln Pro Lys Lys
      50             55             60

ggc cag gga acg gca gca aca gga aat cag gca aca cca aaa aca gca  240
Gly Gln Gly Thr Ala Ala Thr Gly Asn Gln Ala Thr Pro Lys Thr Ala
      65             70             75             80

cca gcc acc atg agc act ccc acc ata ctg gtc gca aca gca gtc cat  288
Pro Ala Thr Met Ser Thr Pro Thr Ile Leu Val Ala Thr Ala Val His
      85             90             95

gca tat cga tac aca aat ggt caa tat gta aag cag ggc aaa ttt ggt  336
Ala Tyr Arg Tyr Thr Asn Gly Gln Tyr Val Lys Gln Gly Lys Phe Gly
      100            105            110

gct gca gtt ctg ggg aac cac aca gcc aga gag tat agg att ctt ctt  384
Ala Ala Val Leu Gly Asn His Thr Ala Arg Glu Tyr Arg Ile Leu Leu
      115            120            125

tat atc agt caa caa cag cca gtt acg gtt gct agg att cat gtg aac  432
Tyr Ile Ser Gln Gln Gln Pro Val Thr Val Ala Arg Ile His Val Asn
      130            135            140

ttt gag cta atg gtt cgg ccc aat aac tat agc acc ttt tat gat gac  480
Phe Glu Leu Met Val Arg Pro Asn Asn Tyr Ser Thr Phe Tyr Asp Asp
      145            150            155            160

cag aga cag aac tgg tcc atc atg ttt gag tcg gaa aag gct gct gtg  528
Gln Arg Gln Asn Trp Ser Ile Met Phe Glu Ser Glu Lys Ala Ala Val
      165            170            175

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-9-

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ctg gat gca gtg ctc tcc cag gac ctc att gtg gca gac ggc cct gct Leu Asp Ala Val Leu Ser Gln Asp Leu Ile Val Ala Asp Gly Pro Ala 195 200 205	624
gta gaa gtt gga gat tct ttg gaa gtg gcc tat acc ggc tgg ctc ttt Val Glu Val Gly Asp Ser Leu Glu Val Ala Tyr Thr Gly Trp Leu Phe 210 215 220	672
cag aat cat gtg ctg ggc cag gtt ttc gac tcc act gct aac aaa gat Gln Asn His Val Leu Gly Gln Val Phe Asp Ser Thr Ala Asn Lys Asp 225 230 235 240	720
aag ttg ctt cgc ttg aag tta gga tca gga aaa gtc atc aag ggc tgg Lys Leu Leu Arg Leu Lys Leu Gly Ser Gly Lys Val Ile Lys Gly Trp 245 250 255	768
gag gat gga atg ctg ggc atg aaa aaa gga gga aag cga ttg ctt att Glu Asp Gly Met Leu Gly Met Lys Lys Gly Gly Lys Arg Leu Leu Ile 260 265 270	816
gtc cct cca gcc tgt gct gtt ggc tca gaa ggg gta ata ggc tgg act Val Pro Pro Ala Cys Ala Val Gly Ser Glu Gly Val Ile Gly Trp Thr 275 280 285	864
caa gca acg gac tcg atc ctg gtg ttc gag gtg gag gtt agg cgg gtg Gln Ala Thr Asp Ser Ile Leu Val Phe Glu Val Glu Val Arg Arg Val 290 295 300	912
aag ttt gcc aga gat tct ggc tct gat ggt cac agt gtt agt tcc cgc Lys Phe Ala Arg Asp Ser Gly Ser Asp Gly His Ser Val Ser Ser Arg 305 310 315 320	960
gat tct gca gct ccg tct ccc atc cct ggt gct gac aac ctc tct gct Asp Ser Ala Ala Pro Ser Pro Ile Pro Gly Ala Asp Asn Leu Ser Ala 325 330 335	1008
gat cct gtt gtg tca cca ccc aca tca ata cct ttc aaa tca ggg gag Asp Pro Val Val Ser Pro Pro Thr Ser Ile Pro Phe Lys Ser Gly Glu 340 345 350	1056
cca gct ctt cgt acc aaa tct aac tcc ctc agt gaa caa ctt gca ata Pro Ala Leu Arg Thr Lys Ser Asn Ser Leu Ser Glu Gln Leu Ala Ile 355 360 365	1104
aat aca agt ccc gat gca gtc aaa gcc aag ttg atc tct cgg atg gct Asn Thr Ser Pro Asp Ala Val Lys Ala Lys Leu Ile Ser Arg Met Ala 370 375 380	1152
aaa atg ggc cag ccc atg ctg ccc atc ctt cca cca cag ctg gat tcc Lys Met Gly Gln Pro Met Leu Pro Ile Leu Pro Pro Gln Leu Asp Ser 385 390 395 400	1200

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cct gtg gtg act ccg tcc gtc cag ccc tct ctt cag ccg gcc cat cca Pro Val Val Thr Pro Ser Val Gln Pro Ser Leu Gln Pro Ala His Pro	1296
420 425 430	
gcg tta cca cag atg acc tca cag gca cct cag cca tct gtt act ggg Ala Leu Pro Gln Met Thr Ser Gln Ala Pro Gln Pro Ser Val Thr Gly	1344
435 440 445	
ctc cag gca cct tct gct gcc tta atg caa gtg tca tct ctc gat tcc Leu Gln Ala Pro Ser Ala Ala Leu Met Gln Val Ser Ser Leu Asp Ser	1392
450 455 460	
cac tca gct gta tct gga aat gcc caa tcc ttt cag ccc tat gca ggt His Ser Ala Val Ser Gly Asn Ala Gln Ser Phe Gln Pro Tyr Ala Gly	1440
465 470 475 480	
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485 490 495	
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530 535 540	
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545 550 555 560	
ggc aat tcc atg ctt att cct agc atg tca gtt aca atg gaa aca agc Gly Asn Ser Met Leu Ile Pro Ser Met Ser Val Thr Met Glu Thr Ser	1728
565 570 575	
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580 585 590	
aag caa gag atc ctt gaa aag agc aat cgg ata gaa gaa cag aat gac Lys Gln Glu Ile Leu Glu Lys Ser Asn Arg Ile Glu Glu Gln Asn Asp	1824
595 600 605	
aag att agt gaa cta att gaa cga aat cag agg tat gtt gag cag agt Lys Ile Ser Glu Leu Ile Glu Arg Asn Gln Arg Tyr Val Glu Gln Ser	1872
610 615 620	

-11-

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aca gag gag tta gca gcg gcc act gcg cag gtc tct cat ctg cag ctg Thr Glu Glu Leu Ala Ala Ala Thr Ala Gln Val Ser His Leu Gln Leu 660 665 670	2016
aaa atg act gct cac caa aaa aag gaa aca gag ctg cag atg cag ctg Lys Met Thr Ala His Gln Lys Lys Glu Thr Glu Leu Gln Met Gln Leu 675 680 685	2064
aca gaa agc ctg aag gag aca gat ctt ctc agg ggc cag ctc acc aaa Thr Glu Ser Leu Lys Glu Thr Asp Leu Leu Arg Gly Gln Leu Thr Lys 690 695 700	2112
gtg cag gca aag ctc tca gag ctc caa gaa acc tct gag caa gca cag Val Gln Ala Lys Leu Ser Glu Leu Gln Glu Thr Ser Glu Gln Ala Gln 705 710 715 720	2160
tcc aaa ttc aaa agt gaa aag cag aac cgg aaa caa ctg gaa ctc aag Ser Lys Phe Lys Ser Glu Lys Gln Asn Arg Lys Gln Leu Glu Leu Lys 725 730 735	2208
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gat gag cac ctg cag cag tac cag gag gtg tgc gca cag aga gat gcc Asp Glu His Leu Gln Gln Tyr Gln Glu Val Cys Ala Gln Arg Asp Ala 835 840 845	2544

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-13-

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 1140 1145 1150

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 1170 1175 1180

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 Glu Leu Phe Lys Gly Ala Thr Leu Lys Ala Leu Arg Pro Lys Ala Gln
 1185 1190 1195 1200

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 Leu Gly
 1235

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ggtgagcatt ctgggaacaa tatttgggct cagagggtgg gttggccacc ttctgagccc 3865

caccctcgcc agacctggtg aagaggatca taacctgtc ttcaagaaca ctgggatttc 3925

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tggtagaact aaggagatt acaccatcta aatcccagtg cagtaacag cctggcctat 4165

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35 40 45

His Gly Asn Glu Phe Phe Gln Tyr Thr Ala Pro Lys Gln Pro Lys Lys
50 55 60

Gly Gln Gly Thr Ala Ala Thr Gly Asn Gln Ala Thr Pro Lys Thr Ala
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Pro Ala Thr Met Ser Thr Pro Thr Ile Leu Val Ala Thr Ala Val His
85 90 95

Ala Tyr Arg Tyr Thr Asn Gly Gln Tyr Val Lys Gln Gly Lys Phe Gly
100 105 110

Ala Ala Val Leu Gly Asn His Thr Ala Arg Glu Tyr Arg Ile Leu Leu
115 120 125

Tyr Ile Ser Gln Gln Gln Pro Val Thr Val Ala Arg Ile His Val Asn
130 135 140

Phe Glu Leu Met Val Arg Pro Asn Asn Tyr Ser Thr Phe Tyr Asp Asp
145 150 155 160

Gln Arg Gln Asn Trp Ser Ile Met Phe Glu Ser Glu Lys Ala Ala Val
165 170 175

Glu Phe Asn Lys Gln Val Cys Ile Ala Lys Cys Asn Ser Thr Ser Ser
180 185 190

Leu Asp Ala Val Leu Ser Gln Asp Leu Ile Val Ala Asp Gly Pro Ala
195 200 205

Val Glu Val Gly Asp Ser Leu Glu Val Ala Tyr Thr Gly Trp Leu Phe
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(19) World Intellectual Property Organization
International Bureau



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16 August 2001 (16.08.2001)

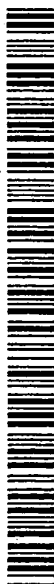
PCT

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WO 01/58937 A3

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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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- Published:
— with international search report
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11 April 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INTERFERON-ALPHA INDUCED GENES

(57) Abstract: The present disclosure relates to identification of genes upregulated by interferon- α administration, in particular the human genes corresponding to the cDNA sequences in GenBank designated g4586459, g2342476, g3327161 and g4529886. Determination of expression products of these genes is proposed as having utility in predicting responsiveness to treatment with interferon- α and other interferons which act at the Type I interferon receptor. Therapeutic use of the proteins encoded by the same genes is also envisaged.



WO 01/58937 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/00541

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/47 C07K16/18 A61K38/17 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBL, EPO-Internal, BIOSIS, WPI Data, CHEM ABS Data, MEDLINE, EMBASE, LIFESCIENCE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No. -
X	<p>DATABASE EMBL 'Online! Accession Nr.: AB025254, 1 April 1999 (1999-04-01) HIROSE T: "CDC2 related kinase, PCTAIRE 2 binding protein that contains tudor domain." XP002168215 see sequence abstract</p> <p style="text-align: center;">--- -/--</p>	1-5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *S* document member of the same patent family

Date of the actual completion of the international search

10 August 2001

Date of mailing of the international search report

03.09.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Bassias, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/00541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL 'Online! Accession Nr.: AB006679, 23 August 1997 (1997-08-23) SHIOSAKA T: "Differential expression of 1-4 gene in functionally distinct ME-1 subclones" XP002174639 see sequence abstract</p>	1-5
X	<p>DATABASE EMBL 'Online! Accession Nr.: AF027733, 8 November 1997 (1997-11-08) BRULE S AND LUSSIER JG: "Bovine ATP binding protein" XP002174640 see sequence abstract</p>	1-5
X	<p>DATABASE EMBL 'Online! Accession Nr.: AB014574, 6 February 1999 (1999-02-06) OHARA O ET AL.: "direct submission" XP002174641 see sequence abstract</p>	1-5
X	<p>DATABASE EMBL 'Online! Accession Nr.: AF134726, 27 March 1999 (1999-03-27) ROWEN L ET AL.: "Sequence of the human major histocompatibility complex class III region" XP002174642 see sequence "GI:4529888" abstract</p>	1-5
X	<p>DATABASE EMBL 'Online! Accession Nr.: AF109906, 10 December 1998 (1998-12-10) ROWEN L ET AL.: "Sequence of the mouse MHC class III region" XP002174643 see sequence "GI3986769" abstract</p>	1-5
X	<p>DATABASE EMBL 'Online! AI828004, 13 July 1999 (1999-07-13) XP002174644 see sequence abstract</p>	2-5

-/-

INTERNATIONAL SEARCH REPORT

Intern 1st Application No

PCT/GB 01/00541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! AA934369, 29 April 1998 (1998-04-29) XP002174645 see sequence abstract	2-5
Y	EP 0 242 329 A (CIBA GEIGY AG) 21 October 1987 (1987-10-21) the whole document, in particular: page 2, first paragraph; page 3, third paragraph; page 4, paragraphs 1-3	1-14
Y	HORISBERGER M A ET AL: "IFN-ALPHA INDUCED HUMAN 78 KD PROTEIN: PURIFICATION AND HOMOLOGIES WITH THE MOUSE MX PROTEIN; PRODUCTION OF MONOCLONAL ANTIBODIES, AND POTENTIATION EFFECT OF IFN-GAMMA" JOURNAL OF INTERFERON RESEARCH, US, MARY ANN LIEBERT, INC., NEW YORK, NY, vol. 7, 1 August 1987 (1987-08-01), pages 331-343, XP002059946 ISSN: 0197-8357 the whole document	1-14
Y	US 5 834 235 A (RICH STEVEN A ET AL) 10 November 1998 (1998-11-10) the whole document, in particular column 1, lines 55-67 and column 2, line 59 - column 3, line 39	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/00541

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-12
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 8-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 8-12

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Claims 1-14 (all partially)

Isolated polypeptide comprising SEQ ID NO: 2, variants and fragments thereof, the corresponding polynucleotide (SEQ ID NO: 1), pharmaceutical compositions comprising said polypeptide or polynucleotide, antibodies and antisense sequences against said molecules and the use of said molecules for preparation of medicaments, for therapy and for prediction of responsiveness of a patient to treatment with a Type I interferon.

2. Claims: Claims 1-14 (all partially)

Isolated polypeptide comprising SEQ ID NO: 4, variants and fragments thereof, the corresponding polynucleotide (SEQ ID NO: 3), pharmaceutical compositions comprising said polypeptide or polynucleotide, antibodies and antisense sequences against said molecules and the use of said molecules for preparation of medicaments, for therapy and for prediction of responsiveness of a patient to treatment with a Type I interferon.

3. Claims: Claims 1-14 (all partially)

Isolated polypeptide comprising SEQ ID NO: 6, variants and fragments thereof, the corresponding polynucleotide (SEQ ID NO: 5), pharmaceutical compositions comprising said polypeptide or polynucleotide, antibodies and antisense sequences against said molecules and the use of said molecules for preparation of medicaments, for therapy and for prediction of responsiveness of a patient to treatment with a Type I interferon.

4. Claims: Claims 1-14 (all partially)

Isolated polypeptide comprising SEQ ID NO: 8, variants and fragments thereof, the corresponding polynucleotide (SEQ ID NO: 7), pharmaceutical compositions comprising said polypeptide or polynucleotide, antibodies and antisense sequences against said molecules and the use of said molecules for preparation of medicaments, for therapy and for prediction of responsiveness of a patient to treatment with a Type I interferon.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/00541

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0242329	A	21-10-1987	AT 125304 T	15-08-1995
			AU 608216 B	28-03-1991
			AU 7151087 A	22-10-1987
			CA 1340289 A	29-12-1998
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			US 5198350 A	30-03-1993
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US 5834235	A	10-11-1998	US 6060279 A	09-05-2000